

**IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE**

CELLECTIS S.A.,

Plaintiff,

v.

PRECISION BIOSCIENCES, INC.,

Defendant.

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C.A. No. 11-173-SLR-MPT

JURY TRIAL DEMANDED

**DEFENDANT PRECISION BIOSCIENCES, INC.'S OPENING MEMORANDUM IN
SUPPORT OF ITS PROPOSED CLAIM CONSTRUCTIONS FOR
U.S. PATENT NO. 7,897,372**

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I. INTRODUCTION

Precision BioSciences, Inc. (“Precision”) submits this Opening Claim Construction Memorandum to address disputes with Cellectis S.A. (“Cellectis”) over the meaning of claim terms in U.S. Patent No. 7,897,372 (“‘372 Patent”, attached as **Exhibit 1**). The asserted claims of the ‘372 Patent are directed to “I-CreI meganuclease variants,” which are artificial enzymes produced by recombinant DNA technology based on a naturally-occurring enzyme called I-CreI, and are useful in genetic engineering technology.

Although there is agreement as to most technical terminology in the claims,¹ Cellectis seeks overly and artificially broad interpretations of key claim phrases in an attempt to cover products of its competitor, Precision. In doing so, however, Cellectis construes the claims of the ‘372 Patent so broadly as to cover subject matter far beyond the scope of anything disclosed in the specification. Because Cellectis’s proposed claim constructions are inconsistent with the scope of the patent disclosure and the plain meaning of the claims as understood by a person of skill in the art – and are, in some instances internally inconsistent – Cellectis’s proposed claim constructions should be rejected. Instead, for the reasons set forth below, the Court should adopt Precision’s proposed claim constructions, which are consistent with the teachings and scope of the patent disclosure, and the plain meaning of the claims as understood by one of ordinary skill in the art.

II. BACKGROUND

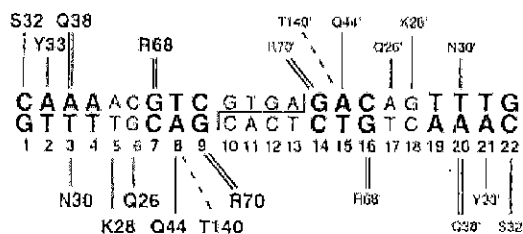
A. I-CreI Meganucleases Variants

Homing endonucleases or *meganucleases* are enzymes that bind (“recognize”) and cut (“cleave”) particular sequences in DNA of between 14 and 40 base pairs in length. The specific

sequences that are bound and cut by these enzymes are called “recognition sequences.”² I-CreI is a naturally-occurring meganuclease that cleaves the following 22-base sequence:

5' - TCAAAACGTCGTGAGACAGTTTGG - 3'
3' - AGTTTTCAGCACTCTGTCAAACC - 5'

(‘372 Patent, col. 16, ll. 20-22; SEQ ID NO: 65; Fig. 2A; Seligman Decl., ¶ 35.) As scientists studied the structure and functional domains of I-CreI, it became apparent that certain amino acid residues within the protein³ were responsible for the sequence-specific binding of the recognition site. For example, Fig. 1 of Seligman *et al.* (2002) included a depiction of the I-CreI recognition site showing the amino acid residues, identified by a single letter representing the amino acid and a number representing the order number of that amino acid in the sequence of 163 that makes up I-CreI, believed to contact each base pair of the DNA, including every residue recited in the claims of the ‘372 Patent:



(Seligman Decl., ¶ 38.) Well before the filing of the applications that issued as the ‘372 Patent, scientists (*e.g.*, Seligman *et al.* (2002); Sussman *et al.* (2004)) had experimented with, and succeeded at, modifying the sequence-specificity of I-CreI by making mutations (or changes) to

¹ A glossary of agreed definitions is appended to the Joint Claim Construction Statement. D.I. 164.

² A “recognition sequence” may also be called a “recognition site,” “target sequence,” “target site,” “homing site,” or “cleavage site.” (Seligman Decl., ¶ 24; ‘372 Patent, col. 6, ll. 22-24.)

³ Like all proteins, the I-CreI enzyme is composed of a string of amino acids, or polypeptide, that folds into a three-dimensional structure based on electrochemical and physicochemical interactions. (Seligman Decl., ¶¶ 20-23.)

the amino acid residues of the “DNA-binding domains” that directly contact the recognition sequence. (Seligman Decl., ¶ 41.)

I-CreI is a member of the “LAGLIDADG” (pronounced “läg'-lē-dädj”) family of meganucleases, which derives its name from a pattern in the amino acid sequence (identified by this sequence of letters representing those amino acids) called the LAGLIDADG motif. In their naturally-occurring forms, LAGLIDADG meganucleases function as proteins containing two LAGLIDADG motifs: Either two LAGLIDADG motifs in a single polypeptide chain, as in di-LAGLIDADG or single-chain meganucleases, or one LAGLIDADG motif in each of two polypeptide monomers that associate to form a homodimer, as in mono-LAGLIDADG meganucleases. (Seligman Decl., ¶ 25.)

In addition to modifying the sequence specificity of I-CreI, well before the applications which issued as the ‘372 Patent, scientists had experimented with making a single-chain version of I-CreI, which naturally occurs as a homodimer of two monomers with a single LAGLIDADG motif (*e.g.*, Epinat *et al.* (2003)), and had succeeded at making a hybrid single-chain meganuclease between a portion of the natural single-chain meganuclease I-DmoI and a portion of the natural homodimer meganuclease I-CreI (*e.g.*, Epinat *et al.* (2003), Chevalier *et al.* (2002)). (Seligman Decl., ¶ 47.)

B. The ‘372 Patent

The ‘372 Patent describes much of the prior art concerning the structure, functional motifs, and modifications of meganucleases, particularly I-CreI, including the work of Seligman *et al.* 2002, Sussman *et al.* 2004, Chevalier *et al.* 2003 and Epinat *et al.* 2003. ‘372 Patent, col. 1, l. 25 to col. 4, l. 25.⁴ After reciting the benefits of creating I-CreI variants with modified sequence specificity for cleaving DNA, the applicants describe a method for preparing I-CreI

variant meganucleases having modified cleavage specificity as compared to an initial meganuclease, which can be naturally-occurring, or “wild-type,” I-CreI or an artificial variant of I-CreI, particularly the “I-CreI D75N” variant described in SEQ ID NO: 70. The method for preparing an I-CreI meganuclease variant, according to the ‘372 patent, involves (1) substituting amino acids at positions corresponding to positions 44, 68, and 70 of wild-type I-CreI and (2) selecting variants with a set of recognition sequences or cleavage profile that conforms to a specific formula. ‘372 Patent, col. 4, l. 48 to col. 5, l. 35.

As described in detail below, the ‘372 Patent claims these I-CreI meganuclease variants as monomers, as homodimers (two identical monomers associated to form a dimer), heterodimers (two different monomers associated to form a dimer), and single-chain meganucleases (two different monomers “fused” together in a single polypeptide).

III. BASIC PRINCIPLES OF CLAIM CONSTRUCTION

Claim construction is a question of law for the court. *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 970-71 (Fed. Cir. 1995) (*en banc*), *aff’d.*, 517 U.S. 370 (1996). Claim terms are generally given their ordinary and customary meaning as understood by “a person of ordinary skill in the art in question at the time of the invention.” *Phillips v. AWH Corp.*, 415 F.3d 1303, 1313 (Fed. Cir. 2005) (*en banc*). As the Federal Circuit noted in *Phillips*, however:

The claims, of course, do not stand alone. Rather, they are part of a fully integrated written instrument, consisting principally of a specification that concludes with the claims. For that reason, claims must be read in view of the specification, of which they are a part. . . . [T]he specification is always highly relevant to the claim construction analysis. Usually, it is dispositive; it is the single best guide to the meaning of a disputed term.

415 F.3d at 1315 (quotations omitted); *see also Merck & Co. v. Teva Pharms. USA, Inc.*, 347 F.3d 1367, 1371 (Fed. Cir. 2003) (quotations omitted) (“A fundamental rule of claim

⁴ Additional relevant prior art has been identified by Precision BioSciences.

construction is that terms in a patent document are construed with the meaning with which they are presented in the patent document. Thus claims must be construed so as to be consistent with the specification, of which they are a part.”).

Moreover, “[b]ecause the meaning of a claim term as understood by persons of skill in the art is often not immediately apparent . . . the court looks to ‘those sources available to the public that show what a person of skill in the art would have understood [the] disputed claim language to mean.’” *Phillips*, at 415 F.3d at 1314 (quoting *Innova/Pure Water, Inc. v. Safari Water Filtration Systems, Inc.*, 381 F.3d 1111, 1116 (Fed. Cir. 2004)).

While “the best source for understanding a technical term is the specification from which it arose,” *Multiform Desiccants, Inc. v. Medzam, Ltd.*, 133 F.3d 1473, 1478 (Fed. Cir. 1998), the Federal Circuit has “also authorized district courts to rely on extrinsic evidence, which consists of all evidence external to the patent and prosecution history, including expert and inventor testimony, dictionaries, and learned treatises.” *Phillips*, 415 F.3d at 1317 (quotation omitted). In particular, expert testimony may be used “to provide background on the technology at issue, to explain how an invention works, to ensure that the court’s understanding of the technical aspects of the patent is consistent with that of a person of skill in the art, or to establish that a particular term in the patent or the prior art has a particular meaning in the pertinent field.” *Id.* “However, conclusory, unsupported assertions by experts as to the definition of a claim term are not useful to a court. Similarly, a court should discount any expert testimony that is clearly at odds with the claim construction mandated by the claims themselves, the written description, and the prosecution history, in other words, with the written record of the patent.” *Id.* (quotation omitted).

Where a claim is not amenable to construction, it is indefinite under 35 U.S.C. § 112, ¶ 2. *See Honeywell Int'l, Inc. v. Int'l Trade Comm'n*, 341 F.3d 1332, 1338 (Fed. Cir. 2003). A claim is indefinite if, for example, the intrinsic evidence fails to provide “any guidance as to what one of ordinary skill in the art would interpret the claim to require.” *Id.* at 1340. In other words, the test for indefiniteness depends on “whether the claim delineates to a skilled artisan the bounds of the invention.” *Talecris Biotherapeutics, Inc. v. Baxter Int'l, Inc.*, 510 F. Supp. 2d 356, 359 (D. Del. 2007).

IV. ANALYSIS OF DISPUTED CLAIM TERMS

Collectis contends that Precision infringes at least claims 1-8, 10, 12-14, 16, 18-26, 28, 30-32, 34, 36-44, 46, 48-50, 52, and 54 of the '372 Patent, and Precision contends that all claims of the '372 Patent are invalid. Claims 1, 19 and 37 are the only independent claims of the '372 Patent and are identical except for the alternative recitations of “isolated,” “purified” and “recombinant,” respectively, in describing the claimed monomers of an I-CreI variant. Because the parties do not dispute the meanings of the terms “isolated,” “purified” and “recombinant,” there is no need to separately construe claims 1, 19, and 37, and they will therefore be addressed together. Likewise, claims 2-18, claims 20-36 and claims 38-54 are identical except that claims 2-18 depend from claim 1, claims 20-36 depend from claim 19, and claims 38-54 depend from claim 37. Claims 2-18, claims 20-36 and claims 38-54 will therefore also be addressed together. The claims of the '372 Patent are shown in Exhibit 2 with disputed terms emphasized.

The parties' claim constructions for each of the disputed terms are set forth in the Joint Claim Construction Statement, and each of these terms is discussed separately below.

A. “monomer of an I-CreI meganuclease variant” (All Asserted Claims)

Claim Term	Collectis's Proposed Construction	Precision's Proposed Construction
“monomer of an	a polypeptide from an I-CreI	one of two polypeptides, each

I-CreI mega-nuclease variant”	meganuclease variant	having a single copy of the dodecapeptide (LAGLIDADG) motif, that can act together to form an I-CreI variant homodimer
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1. Key Issues

Precision has set forth a definition of “monomer of an I-CreI meganuclease variant” which should aid the jury in distinguishing a “monomer” from the other forms of I-CreI meganuclease proteins described in the ‘372 Patent: homodimers, heterodimers and single-chain mega-nucleases. Precision’s definition includes the plain language meaning that a monomer must be part of a dimer, or “one of two polypeptides ... that can act together to form ... [a] homodimer.” In addition, it incorporates the necessary requirements that (a) a monomer “of an I-CreI meganuclease” must include “a single copy of the dodecapeptide (LAGLIDADG) motif,” to distinguish from single-chain I-CreI meganuclease variants which have two copies, and (b) two such monomers can form an I-CreI variant homodimer, to distinguish from other homodimers.

In contrast, Collectis proposes a definition of a monomer which includes none of the characteristics that distinguish a monomer from a single-chain meganuclease. Moreover, Collectis defines a “monomer of” as a “polypeptide from an I-CreI meganuclease variant.” On its face, this definition would include anything from just a few amino acids selected from an I-CreI monomer sequence to an entire single-chain I-CreI meganuclease sequence of over 300 amino acids. Because Collectis’s definition does not suggest in any way that the monomer is only one of two polypeptides that act together to form a dimer or that it includes just one LAGLIDADG motif, it does not clearly exclude from its scope the other fragments of an I-CreI monomer that may not include its key LAGLIDADG motif or, at the opposite extreme, entire single-chain meganucleases that include two LAGLIDADG motifs.

2. Precision's Construction is Supported by the Claim Language.

Support for Precision's claim construction can be found in the claims of the '372 Patent themselves. For example, claims 1, 19 and 37 recite that the monomer "compris[es] at least one mutation in the amino acid sequence of SEQ ID NO: 70." As explained below, Precision interprets this limitation as requiring that the monomer has the amino acid sequence set forth in SEQ ID NO: 70 except for the mutations specified in the claims. SEQ ID NO: 70 is clearly an I-CreI monomer, having a single copy of the LAGLIDADG motif, and two copies of the monomer are capable of forming an I-CreI variant homodimer. (Seligman Decl., ¶¶ 53-56.) In addition, the last clause of claims 1, 19, 70 recites that "said monomer when in a dimeric form is able to cleave DNA," indicating that the monomer must be able to form a functional I-CreI variant homodimer when two such polypeptides act together. Similarly, claims 4, 22 and 40 recite that the "monomer when in a dimeric form has a modified DNA cleavage specificity," indicating again that the "monomer" must be one of two polypeptides capable of forming an I-CreI variant homodimer. Furthermore, claims 6, 24 and 42 recite I-CreI meganuclease homodimers, and claims 7-12, claims 25-30 and claims 43-48 recite I-CreI meganuclease heterodimers, all of which comprise a "monomer" according to claims 1, 19 or 37, indicating again that the "monomer" must be one of two polypeptides capable of forming a homodimer or heterodimer. Finally, claims 13-18, claims 31-35 and claims 49-54 recite a single-chain chimeric meganuclease comprising a "monomer" according to claims 1, 19 or 37 and a second monomer, indicating again that the "monomer" is not an entire single-chain meganuclease and includes only one of the two LAGLIDADG motifs found in a single-chain meganuclease.

Thus, the context of the claims themselves makes clear that the elements of Precision's proposed construction for the term "monomer" are not only consistent with the usage of the term in the claims, but are necessary to define the term in a manner consistent with the claims.

3. Precision's Construction is Supported by the Specification.

Support for Precision's claim construction also can be found in the specification of the '372 Patent. For example, at col. 1, l. 53 - col. 2, l. 3, the '372 patent teaches (emphasis added):

Homing endonucleases fall into 4 separated families on the basis of pretty well conserved amino acids motifs [for review, see Chevalier and Stoddard (Nucleic Acids Research, 2001, 29, 3757-3774)]. One of them is the dodecapeptide family (dodecamer, DOD, D1 -D2, LAGLIDADG (SEQ ID NO: 91), P1 -P2). This is the largest family of proteins clustered by their most general conserved sequence motif: one or two copies (vast majority) of a twelve-residue sequence: the dodecapeptide. Homing endonucleases with one dodecapeptide (D) are around 20 kDa in molecular mass and act as homodimers. Those with two copies (DD) range from 25 kDa (230 amino acids) to 50 kDa (HO, 545 amino acids) with 70 to 150 residues between each motif and act as monomer. Cleavage is inside the recognition site, leaving 4 nt staggered cut with 3'OH overhangs. Enzymes that contain a single copy of the LAGLIDADG (SEQ ID NO: 91) motif, such as I-CeuI and I-CreI act as homodimers and recognize a nearly palindromic homing site.

Thus, the specification makes clear that a monomer of an I-CreI meganuclease is one of two polypeptides which act together as a homodimer, and have a single copy of the LAGLIDADG motif, thus distinguishing them from LAGLIDADG meganucleases that have two copies of the LAGLIDADG motif and act as a monomer (*i.e.*, single-chain).

4. Collectis's Construction Should Be Rejected.

In contrast, Collectis's proposed construction of "monomer of" an I-CreI variant as "a polypeptide from" an I-CreI variant is without support in the claims or specification, and does not in any way describe a monomer. Because Collectis's proposed construction would not distinguish a monomer from an I-CreI homodimer or I-CreI heterodimer from a single-chain I-CreI meganuclease, and thus would not distinguish I-CreI variant monomers containing one LAGLIDADG motif from single-chain I-CreI meganucleases containing two LAGLIDADG motifs in a single polypeptide, it fails to clarify the claim term monomer in any way. Moreover, the description of the monomer as a "polypeptide from" an I-CreI meganuclease variant creates

ambiguity as to whether the monomer may be an incomplete fragment of an I-CreI variant

monomer lacking a functional LAGLIDADG motif or other required structural domain.

- B. “[monomer of an I-CreI meganuclease variant] comprising at least one mutation in the amino acid sequence of SEQ ID NO: 70, wherein said at least one mutation comprises a substitution at one or more of the amino acids residues at positions 44, 68 and 70 and said monomer further comprises at least one additional mutation of an amino acid residue directly contacting a DNA target sequence wherein said amino acid residue is selected from the group consisting of positions 26, 28, 30, 32, 33, and 38” (All Asserted Claims)**

Claim Term	Collectis’s Proposed Construction	Precision’s Proposed Construction
“[monomer of an I-CreI meganuclease variant] comprising at least one mutation in the amino acid sequence of SEQ ID NO: 70, wherein said at least one mutation comprises a substitution at one or more of the amino acids residues at positions 44, 68 and 70 and said monomer further comprises at least one additional mutation of an amino acid residue directly contacting a DNA target sequence wherein said amino acid residue directly contacting a DNA target sequence is selected from the group consisting of positions 26, 28, 30, 32, 33, and 38”	monomer of an I-CreI meganuclease variant comprising at least one mutation in the amino acid sequence of SEQ ID NO: 70, wherein said at least one mutation comprises a substitution at one or more of the amino acid residues at positions 44, 68 and 70 with reference to the amino acid numbering of SwissProt accession number P05725 or pdb accession code 1g9y and said monomer further comprises at least one additional mutation of an amino acid residue at positions 26, 28, 30, 32, 33 or 38 with reference to the amino acid numbering of SwissProt accession number P05725 or pdb accession code 1g9y	a meganuclease having the amino acid sequence of SEQ ID NO: 70 in which from 1-3 of the amino acids corresponding to positions 44, 68 and 70 of wild-type I-CreI and from 1-6 of the amino acids corresponding to positions 26, 28, 30, 32, 33 and 38 of wild-type I-CreI have been substituted with different amino acids

1. Key Issues

The key issue in this claim construction is whether the claims should be construed to cover the monomers of I-CreI meganuclease variants that are disclosed or described in the specification of the ‘372 Patent, or whether the claims should encompass an unlimited number of variants with an unlimited number of mutations at unlimited positions in SEQ ID NO: 70.

Precision has set forth a definition of the claim language that is consistent with every single meganuclease disclosed or described in the '372 Patent and that should aid the jury in distinguishing variants with mutations at the amino acid positions identified compared to the SEQ ID NO: 70 baseline that are within the scope of the invention from arbitrary variants having unlimited numbers of mutations at unlimited amino acid positions. In addition, Precision's definition includes the plain meaning of the claim: The variants include from one to three mutations at the three positions corresponding to positions 44, 68 and 70 of wild-type I-CreI, and from one to six mutations at the six positions corresponding to positions 26, 28, 30, 32, 33 and 38 of wild-type I-CreI. Moreover, Precision's construction of this claim term gives meaning to the limitation "SEQ ID NO: 70" by requiring that the variants have or include the amino acid sequence of SEQ ID NO: 70 except for the mutations which are specifically recited in the claim. This can be illustrated by substituting "Xaa" in SEQ ID NO: 70 to indicate a substitution of some unspecified amino acid at each of the nine amino acid positions 26, 28, 30, 32, 33, 38, 44, 68 and 70 recited in the claims of the '372 Patent⁵:

Met	Ala	Asn	Thr	Lys	Tyr	Asn	Lys	Glu	Phe	Leu	Leu	Tyr	Leu	Ala	Gly
	*				5					10					15
Phe	Val	Asp	Gly	Asp	Gly	Ser	Ile	Ile	Ala	Xaa	Ile	Xaa	Pro	Xaa	Gln
				20					25	26		28		30	
Xaa	Xaa	Lys	Phe	Lys	His	Xaa	Leu	Ser	Leu	Thr	Phe	Xaa	Val	Thr	Gln
32	33		35			38		40				44	45		
Lys	Thr	Gln	Arg	Arg	Trp	Phe	Leu	Asp	Lys	Leu	Val	Asp	Glu	Ile	Gly
		50					55					60			
Val	Gly	Tyr	Val	Xaa	Asp	Xaa	Gly	Ser	Val	Ser	Asn	Tyr	Ile	Leu	Ser
	65			68		70					*75				
Glu	Ile	Lys	Pro	Leu	His	Asn	Phe	Leu	Thr	Gln	Leu	Gln	Pro	Phe	Leu
80					85					90					95

⁵ Both parties agree that the references in the claims to "positions 44, 68 and 70" and "positions 26, 28, 30, 32, 33 and 38" actually refer to those positions in wild-type I-CreI, and that the corresponding positions in SEQ ID NO: 70 are positions 45, 69 and 71 and positions 27, 29, 31, 33, 34 and 39. An insertion of one additional amino acid (Ala or A) at position 2 of SEQ ID NO: 70 resulted in this +1 shift in the numbering of the subsequent amino acids of SEQ ID NO: 70 relative to I-CreI. For simplicity, this extra amino acid is not counted to maintain the numbering of wild-type I-CreI. SEQ ID NO: 70 also includes the substitution of Asn for Asp at position 75 (*i.e.*, D75N) and three additional amino acids (Ala-Ala-Asp) at the end of the sequence. All of the changes relative to wild-type I-CreI are marked with asterisks. The positions that may be substituted according to the claims are in bold.

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Lys Leu Lys Gln Lys Gln Ala Asn Leu Val Leu Lys Ile Ile Glu Gln
      100      105      110
Leu Pro Ser Ala Lys Glu Ser Pro Asp Lys Phe Leu Glu Val Cys Thr
      115      120      125
Trp Val Asp Gln Ile Ala Ala Leu Asn Asp Ser Lys Thr Arg Lys Thr
      130      135      140
Thr Ser Glu Thr Val Arg Ala Val Leu Asp Ser Leu Ser Glu Lys Lys
      145      150      155
Lys Ser Ser Pro Ala Ala Asp
160      163 * * *

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In contrast, although Collectis's claim construction also requires from one to three mutations in the three positions corresponding to positions 44, 68 and 70 of wild-type I-CreI, and from one to six mutations in the six positions corresponding to position 26, 28, 30, 32, 33 and 38 of wild-type I-CreI, Collectis suggests that the use of the word "comprising" in the phrase "comprising at least one mutation in the amino acid sequence of SEQ ID NO: 70" is open-ended, and allows for an unlimited number of mutations at unlimited positions in SEQ ID NO: 70. Indeed, under Collectis's construction, no particular amino acid at any position of SEQ ID NO: 70 is required to be maintained in the variant, and thus none are. It would necessarily follow that SEQ ID NO: 70 is completely irrelevant, and ceases to be a claim limitation. This can be illustrated, *without exaggeration*, as follows:

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Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
      5      10      15
Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
      20      25      30
Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
      35      40      45
Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
      50      55      60
Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
      65      70      75
Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
      80      85      90      95
Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
      100      105      110
Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
      115      120      125
Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
      130      135      140
Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
      145      150      155
Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
160      163

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Collectis may argue that one of skill in the art would understand that an "I-CreI meganuclease variant" should not include an "unlimited" number of mutations at "unlimited"

positions. But whether or not one of skill in the art could set some limits on the numbers or positions of acceptable mutations in an I-CreI meganuclease variant, or would, to paraphrase Justice Stewart, “know it when he or she sees it,” is not sufficient. The second paragraph of 35 U.S.C. §112 demands more: “The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.” Collectis’s proposed claim construction fails this test.

Finally, Collectis will likely argue that it is well-established that the transitional phrase “comprising” is generally interpreted as open-ended or inclusive, and does not limit the claim to the elements recited. Although this may be true as a general matter, “[c]omprising” is not a weasel word with which to abrogate claim limitations.” *Spectrum Int’l, Inc. v. Sterilite Corp.*, 164 F.3d 1372, 1380 (Fed. Cir. 1998).

(i) The “wherein” clause limits the “at least one” clause

The claim recites a “monomer of an I-CreI meganuclease variant comprising at least one mutation in the amino acid sequence of SEQ ID NO: 70, wherein said at least one mutation comprises a substitution at one or more of the amino acids residues at positions 44, 68 and 70.” Note that the “at least one mutation” clause is limited by the “wherein” clause such that the mutations in SEQ ID NO: 70 can only be at one or more of positions 44, 68 and 70. Thus, Precision submits that this limitation should be understood as “comprising at least one substitution in the amino acid sequence of SEQ ID NO: 70 at one or more of positions 44, 68 and 70.”

(ii) The “comprising . . . SEQ ID NO: 70” clause requires that amino acid sequence except for the specifically described mutations

The claim recites a “monomer of an I-CreI meganuclease variant comprising at least one mutation in the amino acid sequence of SEQ ID NO: 70.” In order for the mutations to be “in”

that sequence, the amino acid sequence of SEQ ID NO: 70 must be present. This follows from the fact that a meganuclease cannot simply “comprise mutations”; it must comprise some initial or reference sequence in which the mutations (or substitutions) must be made. Thus, this “comprising” limitation should be read as “comprising at least one substitution in the amino acid sequence of SEQ ID NO: 70 at one or more of the amino acids residues at positions 44, 68 and 70.”

(iii) The limitation to “SEQ ID NO: 70” must be given weight

The principles of claim interpretation require that the limitation to “SEQ ID NO: 70” must be given weight. If, however, the limitation to a variant “comprising at least one mutation in the amino acid sequence of SEQ ID NO: 70” is read as permitting an unlimited number of substitutions at unlimited positions in SEQ ID NO: 70, then the limitation to SEQ ID NO: 70 has no weight, as mutations can be made which transform SEQ ID NO: 70 into any other sequence, bearing no relationship whatsoever to SEQ ID NO: 70.

2. Precision’s Construction is Supported by the Plain Meaning of the Claims.

It is undeniable that claims 1, 19 and 37 recite the term “SEQ ID NO: 70,” and that these claims recite “at least one mutation in the amino acid sequence of SEQ ID NO: 70.” Therefore, Precision submits that the plain meanings of these terms are that the claimed monomers of an I-CreI meganuclease variant comprise SEQ ID NO: 70 with the specified one to three mutations at amino acids corresponding to positions 44, 68 and 70 of wild-type I-CreI and one to six mutations at amino acids corresponding to positions 26, 28, 30, 32, 33 and 38.

3. Precision's Construction is Supported by the Specification

As noted above, SEQ ID NO: 70 is necessary to provide context for the numbering of the amino acid residues in the claimed I-CreI meganuclease variants. For example, the specification teaches at col. 5, ll. 44-54 (emphasis added):

In the present invention, unless otherwise mentioned, the residue numbers refer to the amino acid numbering of the I-CreI sequence SWISSPROT P05725 or the pdb accession code 1g9y. According to this definition, a variant named "ADR" is I-CreI meganuclease in which amino acid residues Q44 and R68 have been replaced by alanine and aspartic acid, respectively, while R70 has not been replaced. Other mutations that do not alter the cleavage activity of the variant are not indicated and the nomenclature adopted here does not limit the mutations to the only three positions 44, 68 and 70.

This is consistent with Precision's construction in which amino acids at "positions 44, 68 and 70" and "positions 26, 28, 30, 32, 33 and 38" are interpreted as amino acids corresponding to those positions in wild-type I-CreI.

Furthermore, the specification limits the possible mutations to positions 44, 68 and 70 in several instances, but never suggests that mutations can be made at other positions. For example, the specification of the '372 Patent states at col. 10, l. 63 - col. 11, l. 3 (emphasis added):

The subject-matter of the present invention is also I-CreI meganuclease variants: Obtainable by the method of preparation as defined above; Having one mutation of at least one of the amino acid residues in positions 44, 68 and 70 of I-CreI; said mutations may be the only ones within the amino acids contacting directly the DNA target; and Having a modified cleavage specificity in positions ± 3 to 5.

Similarly, the specification of the '372 Patent states at col. 11, ll. 11-13 (emphasis added):

The I-CreI meganuclease variants according to the invention are mutated only at positions 44, 68 and/or 70 of the DNA binding domain.

Finally, the specification does not disclose or describe even a single embodiment in which there are mutations in SEQ ID NO: 70 other than one to three mutations corresponding to positions 44,

68 and 70. Therefore, this definition is consistent with every single meganuclease disclosed or described in the '372 Patent.

4. Collectis's Construction Should Be Rejected.

Collectis appears to base its construction not on the plain meaning of the claim language or the teachings of the specification, but entirely on the word "comprising." The mere use of the word comprising, however, does not end the inquiry. In an *Ex Parte* Reexamination proceeding requested by Precision (U.S. Reexam Control No. 90/011,806) relating to a very similar Collectis patent (U.S. Pat. No. 7,842,489, "the '489 Patent," **Ex. 4**) whose inventors include all six of the alleged inventors of the '372 Patent,⁶ Precision filed a petition (Petition, **Ex. 5**) seeking review of an initial denial of Precision's request for reexamination and seeking a claim construction from the United States Patent and Trademark Office ("USPTO") to interpret similarly worded claims. In a decision granting the petition (Decision, **Ex. 6**), the Director of the Central Reexamination Unit stated the following (Decision, p. 6, last para. – p. 7, para. 2; emphasis added):

The petition on pages 19-21 correctly discusses the scope of the claims in the '489 patent. The interpretation of claim 1 is that the variants are limited to specific numbers of substitutions of amino acids. Claim 1 is actually a single chain homing endonuclease protein comprising two I-CreI variants, both of which use SEQ ID NO:23 as a starting point amino acid sequence to be modified at specific amino acid residues found in the ranges noted. As detailed in the petition, "it is not reasonable to interpret the claim to include variants having unlimited numbers of substitutions." Claim 1 clearly limits the first variant of I-CreI to "one to six substitutions in the sequence of amino acid residues 26 to 40 and two to three substitutions in the sequence of amino acid residues 44 to 77." Further, the first variant must contain substitutions at positions 33, 68 and 77, a claim limitation that makes this the minimum embodiment for the first variant of I-CreI. The maximum number of amino acid substitutions in the first variant is nine, the sum of six plus three.

⁶ The face of the '372 Patent includes Philippe Duchateau and Frederic Paques as inventors; Collectis has petitioned to add Sylvain Arnould, Patrick Chames, Jean-Charles Epinat, and Emmanuel Lacroix.

For the second variant of I-CreI, the claim is similarly explicit. The second variant of I-CreI contains “four to six substitutions in the sequence of amino acid residues 44 to 77.” Further, the second variant must contain substitutions at positions 26, 30, 32, 38, 44 and 68, a claim limitation that makes this the minimum embodiment for the second variant of I-CreI. The maximum number of amino acid substitutions in the second variant is also nine, the sum of six plus three. Given this claim interpretation, **the scope of the variants claimed is clearly specific and does not embrace unlimited substitution or deletion mutants.** Particularly, claim 1 contains the transitional phrase “...single chain homing endonuclease, comprising a first variant of I-CreI having the amino acid sequence of SEQ ID NO:23 and a second variant of I-CreI having the amino acid sequence of SEQ ID NO:23 in a single polypeptide...” Transitional phrases such as “having” must be interpreted in light of the specification to determine whether open or closed claim language is intended. See MPEP 2111.03. **The patent specification does not describe unlimited substitution or deletion mutant, but rather provides for replacing specific amino acid residues only.** See the ‘489 patent (Ex. 4) at columns 11 and 12 therein.

In the ‘489 Patent, claim 1 read as follows (emphasis added):

1. A single chain homing endonuclease, comprising a **first variant of I-CreI having the amino acid sequence of SEQ ID NO:23** and a **second variant of I-CreI having the amino acid sequence of SEQ ID NO:23** in a single polypeptide, wherein **said first variant of I-CreI contains the following substitutions: one to six substitutions in the sequence of amino acid residues 26 to 40** and two to three substitutions **in the sequence of amino acid residues 44 to 77**, wherein in said first variant of I-CreI there is a substitution at positions 33, 68 and 77, and independently, **said second variant of I-CreI contains the following substitutions: four to six substitutions in the sequence of amino acid residues 26 to 40** and two to three **substitutions in the sequence of amino acid residues 44 to 77**, wherein in said second variant of I-CreI there is a substitution at positions 26, 30, 32, 38, 44, and 68, wherein the endonuclease binds and cleaves DNA.

Thus, as in claims 1, 19 and 37 of the ‘372 Patent, claim 1 of the ‘489 Patent specifies a “scaffold” or “initial” amino acid sequence (SEQ ID NO: 23 in the ‘489 Patent, and SEQ ID NO: 70 in the ‘372 Patent) and specifies certain substitutions at certain positions (e.g., two to three substitutions at positions 44-70 in the ‘489 Patent, and one to three substitutions at positions 44, 68 and 70 in the ‘372 Patent). The choice and ordering of words differ slightly in

the two patents (*e.g.*, “variant . . . having the amino acid sequence of SEQ ID NO:23 . . . contains . . . substitutions . . . in the sequence” in the ‘489 Patent, and “variant comprising . . . mutation in the amino acid sequence of SEQ ID NO: 70 . . . mutation comprises a substitution” in the ‘372 Patent), but the intent is the same: The variants comprise a reference amino acid sequence in which a specifically limited number of mutations/substitutions are made at specifically limited positions, and the USPTO’s construction in this context is instructive.

Finally, Precision notes that Cellectis’s proposed constriction of this term needlessly recites “positions . . . with reference to the amino acid numbering of SwissProt accession number P05725” rather than simply reciting “positions . . . of wild-type I-CreI.” The parties have agreed that the term “wild-type monomer of I-CreI” means “a monomer having the amino acid sequence of SwissProt accession number P05725 or pdb accession code 1g9y.” Therefore, Precision submits that this aspect of Cellectis’s construction is unnecessarily complicated and would not aid the jury in interpreting the claims.

C. “modified DNA cleavage specificity relative to the I-CreI meganuclease of SEQ ID NO: 70 in at least one nucleotide in the +/- 3 to 5 triplets” (Claims 4, 22, 40)

Claim Term	Cellectis’s Proposed Construction	Precision’s Proposed Construction
“modified DNA cleavage specificity relative to the I-CreI meganuclease of SEQ ID NO: 70 in at least one nucleotide in the +/- 3 to 5 triplets”	having the ability to cleave a DNA target site that has at least one nucleotide mutation in the gtc triplet at positions -5 to -3 or the gac triplet at positions +3 to +5, where the DNA target site is not cleaved in the same conditions by an initial meganuclease scaffold	having cleavage specificity for a DNA target having the nucleotide sequence 5'-R ₁ CAAAR ₂ R ₃ R ₄ R' ₄ R' ₃ R' ₂ TTTG R' ₁ -3' where R ₁ is any sequence of 0-9 of the nucleotides g, t, c and a; R ₂ is ac or ct; R ₃ is any sequence of 3 of the nucleotides g, t, c and a except gtc, gcc, gtg, gtt and gct; R ₄ is gt or tc; R' ₄ is ga or ac; R' ₃ is any sequence of 3 of the

		nucleotides g, t, c and a except gac, ggc, cac, aac, and agc; ⁷ R' ₂ is ag or gt; and R' ₁ is any sequence of 0-9 of the nucleotides g, t, c and a
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1. Key Issues

The specification of the '372 patent clearly explains that the I-CreI meganuclease variants of the invention are the result of the methods of the invention. For example, the '372 Patent states at col. 1, ll. 13-19 (emphasis added):

The present *invention relates to a method of preparing I-CreI meganuclease variants* having a modified cleavage specificity. The *invention relates also to the I-CreI meganuclease variants obtainable by said method* and to their applications either for cleaving new DNA target or for genetic engineering and genome engineering for non-therapeutic purposes.

Similarly, the '372 Patent states at col. 7, ll. 26-30 (emphasis added):

Unexpectedly, the *I-CreI meganuclease variants, obtainable by the method described above*, i.e. with a "*modified specificity*" . . .

Similarly, the '372 Patent states at col. 8, l. 66 - col. 9, l. 1 (emphasis added):

The subject-matter of the present invention is also the use of a *I-CreI meganuclease variant* as defined here above, i.e. *obtainable by the method as described above* . . .

Similarly, the '372 Patent states at col. 10, ll. 63-65 (emphasis added):

The subject-matter of *the present invention is also I-CreI meganuclease variants: Obtainable by the method of preparation as defined above* . . .

As explained in detail below, Precision's proposed claim construction is entirely consistent with the teachings of the specification, and seeks to define the "modified specificity" of the claims in the same precise manner in which it is defined in the specification. Cellectis's proposed construction, in contrast, is so lacking of support in the specification that one must

assume it can only be understood to be a tactical ploy. Specifically, Collectis seems to have taken an extreme and unsupportable position in the hope that the court might choose a claim interpretation between the parties' two proposals, thus giving Collectis a narrower interpretation than they are seeking, but far more than is merited by a fair interpretation of the claims in light of the specification.

2. Precision's Construction is Supported by the Specification.

As noted above, the specification of the '372 Patent explains clearly that the I-CreI meganuclease variants of the invention are the result of the methods of the invention. The method of the invention, which defines the I-CreI meganuclease variants of the invention, is first described in the '372 Patent at col. 4, l. 48 – col. 5, l. 35 (emphasis added):

Therefore, the subject-matter of the present invention is a method of preparing a I-CreI meganuclease variant having a modified cleavage specificity, said method comprising:

(a) replacing amino acids Q44, R68 and/or R70, in reference with I - CreI pdb accession code 1g9y, with an amino acid selected in the group consisting of A, D, E, G, H, K, N, P, Q, R, S, T and Y;

(b) selecting the I-CreI meganuclease variants obtained in step (a) having at least one of the following R₃ triplet cleaving profile in reference to positions -5 to -3 in a double-strand DNA target, said positions -5 to -3 corresponding to R₃ of the following formula I:

(SEQ ID NO: 92)

5' -R₁CAAAR₂R₃R₄R'₄R'₃R'₂TTTGR'₁- 3' ,

wherein:

R₁ is absent or present; and when present represents a nucleic acid fragment comprising 1 to 9 nucleotides corresponding either to a random nucleic acid sequence or to a fragment of a I-CreI meganuclease homing site situated from position -20 to -12 (from 5' to 3'), R₁ corresponding at least to position -12 of said homing site,

R₂ represents the nucleic acid doublet ac or ct and corresponds to positions -7 to -6 of said homing site,

R₃ represents a nucleic acid triplet corresponding to said positions -5 to -3, selected among g, t, c and a, except the following triplets : gtc,

⁷ The "definition" of R'₃ provided herein by Precision varies slightly from what was submitted in the Joint Claim Construction Statement due to an oversight.

gcc, gtg, gtt and gct; therefore said nucleic acid triplet is preferably selected among the following triplets: ggg, gga, ggt, ggc, gag, gaa, gat, gac, gta, gcg, gca, tgg, tga, tgt, tgc, tag, taa, tat, tac, ttg, tta, ttt, ttc, tcg, tca, tct, tcc, agg, aga, agt, agc, aag, aaa, aat, aac, atg, ata, att, atc, acg, aca, act, acc, cgg, cga, cgt, cgc, cag, caa, cat, cac, ctg, cta, ctt, ctc, ccg, cca, cct and ccc and more preferably among the following triplets: ggg, ggt, ggc, gag, gat, gac, gta, gcg, gca, tag, taa, tat, tac, ttg, ttt, ttc, tcg, tct, tcc, agg, aag, aat, aac, att, atc, act, acc, cag, cat, cac, ctt, ctc, ccg, cct and ccc,

R₄ represents the nucleic acid doublet gt or tc and corresponds to positions -2 to -1 of said homing site,

R'₁ is absent or present, and when present represents a nucleic acid fragment comprising 1 to 9 nucleotides corresponding either to a random nucleic acid sequence or to a fragment of a I-CreI meganuclease homing site situated from position +12 to +20 (from 5' to 3'), R'₁ corresponding at least to position +12 of said homing site,

R'₂ represents the nucleic acid doublet ag or gt, and corresponds to positions +6 to +7 of said homing site,

R'₃ represents a nucleic acid triplet corresponding to said positions +3 to +5, selected among g, t, c, and a; R'₃ being different from gac, ggc, cac, aac, and agc, when R₃ and R'₃ are non-palindromic,

R'₄ represents the nucleic acid doublet ga or ac and corresponds to positions +1 to +2 of said homing site.

The key step in the method is the selecting step (b), in which variants that have a cleavage specificity characterized by “formula I” are selected. Formula I can be simplified somewhat as shown in Precision’s proposed claim construction. (Seligman Decl., ¶¶ 58-59.) Significantly, formula I excludes target sites that are cleaved by SEQ ID NO: 70, which is also referred to in the specification as “I-CreI D75N”, “I-CreI N75” and “I-CreI scaffold protein” (see, e.g., ‘372 Patent, col. 17, ll. 4-14; col. 7, ll. 4-9). Thus, because the method of the invention requires selecting variants that cleave a target which is not cleaved by SEQ ID NO: 70, the variants of the invention include only variants having modified specificity relative to SEQ ID NO: 70.

In particular, formula I defines R₃ as excluding the five nucleotide triplets gtc, gcc, gtg, gtt and gct at positions -5 to -3. These are precisely the five triplets that the specification of the

'372 Patent describes as cleaved by SEQ ID NO: 70 at, for example, col. 6, ll. 56-60 (emphasis added):

The ***I-CreI D75N mutant*** (I-CreI N75) which may also be used as ***scaffold protein*** for making variants with novel specificity ***cleaves*** not only homing sites wherein the palindromic sequence in ***positions -5 to -3*** is ***gtc***, but also ***gcc***, ***gtt***, ***gtg***, or ***gct*** (FIGS. 8 and 9a).

More generally, the '372 Patent teaches the relevance of all limitations of formula I to defining the "modified specificity" of the I-CreI variants of the invention. For example, the '372 Patent teaches at col. 7, lines 17-25 that (emphasis added):

In this approach, ***the homing site, cleaved by the I-CreI meganuclease variant according to the invention*** but not cleaved by the I-CreI scaffold protein, ***is the same as described above and illustrated in FIG. 2, except that the triplet sequence in positions -5 to -3 (corresponding to R₃ in formula I*** and/or triplet sequence in positions +3 to +5 (corresponding to ***R'₃ in formula I*** ***differ from*** the triplet sequence in the same positions in the homing sites cleaved by ***the I-CreI scaffold protein***.

FIG. 2 is reproduced in **Exhibit 3**, and clearly shows nucleotides G, T, C or A at positions -12 and +12, consistent with the definitions of R₁ and R'₁ in formula I; nucleotides CAAA at positions -11 to -8 and nucleotides TTTG at positions +8 to +11, consistent with formula I; nucleotides AC or CT at positions -7 to -6 and nucleotides AG or GT at positions +6 to +7, consistent with R₂ and R'₂ in formula I; nucleotides GT or TC at positions -2 to -1 and GA or AC at positions +1 to +2, R₄ and R'₄ in formula I. Thus, as taught at col. 7, lines 17-25, and Figure 2 of the '372 Patent, formula I represents the DNA target sites "cleaved by the I-CreI meganuclease variant according to the invention" but not cleaved by SEQ ID NO: 70.

In addition, the specification of the '372 Patent specifically embraces formula I as defining the modified specificity of the I-CreI variants of the invention at col. 8, l. 66 – col. 9, l. 9 (emphasis added):

The subject-matter of the present invention is also the use of a ***I-CreI meganuclease variant*** as defined here above, i.e. ***obtainable by the***

method as described above, in vitro or in vivo for non-therapeutic purposes, for cleaving a double strand nucleic acid target comprising at least a 20-24 bp partially palindromic sequence, wherein at least the sequence in positions +/-8 to 11 is palindromic, and the nucleotide triplet in positions -5 to -3 and/or the nucleotide triplet in positions +3 to +5 differs from gtc, gcc, gtg, gtt, and gct, and from gac, ggc, cac, aac and agc, respectively. Formula I describes such a DNA target.

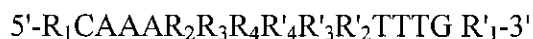
The specification specifically emphasizes the palindromic nucleotides CAAA at positions -11 to -8 and TTTG at positions +8 to +11, and the five triplets excluded at positions -5 to -3 and +3 to +5.

Finally, this claim construction is consistent with every embodiment of an I-CreI meganuclease variant taught in the specification. More important, there is no teaching or suggestion in the specification of any I-CreI meganuclease variant with modified specificity that cleaves any target site which does not comply with the formula I requirements of including CAAA at positions -11 to -8; AC or CT at positions -7 to -6 (R₂); GT or TC at positions -2 to -1 (R₄); GA or AC at positions +1 to +2 (R'₄); AG or GT at position +6 to +7 (R'₂); and TTTG at positions +8 to +11; and which does not cleave a target which differs at positions -5 to -3 from the triplets GTC, GCC, GTG, GTT and GCT (R₃). That is to say, there is no teaching or suggestion in the specification of any I-CreI meganuclease variant with modified specificity that cleaves any target site which does not comply with Precision's proposed claim construction.

3. Collectis's Construction Should Be Rejected.

Aside from the fact that it has no support in the specification, Collectis's proposed construction is most interesting for what it omits: (a) Collectis has omitted any reference to SEQ ID NO: 70, (b) Collectis has omitted four triplets at positions -5 to -3 and four triplets at positions +3 to 5 that the specification teaches are cleaved by SEQ ID NO: 70; and (c) Collectis has omitted any reference to specificity at positions -11 to -6, -2 to +2, and +6 to +11. It would be unsurprising if Collectis were to concede that omissions (a) and (b) are untenable, as any other

position would be unsupportable in view of the specification. The bigger issue, however, is omission (c): The '372 Patent does not teach or suggest any method of producing I-CreI meganuclease variants, and does not disclose any working or prophetic examples of any I-CreI meganuclease variants, in which the target site is not of the form:



where R_1 is any sequence; R_2 is AC or CT; R_4 is GT or TC; R'_4 is GA or AC; R'_2 is AG or GT; and R'_1 is any sequence.

Concrete examples are instructive: The wild-type I-CreI target site, which is also cleaved by SEQ ID NO: 70, is the following (col. 16, ll. 20-22; SEQ ID NO: 65; Fig. 2A):



If the triplet at positions -5 to -3 is changed to ggg, and the triplet at position +5 to +3 is changed to ccc, the sequence becomes:



This sequence is consistent with formula I because R_1 is G; CAAA is present at -11 to -8, R_2 is AC; R_3 is not GTC, GCC, GTG, GTT or GCT; R_4 is GT; R'_4 is GA; R'_3 is not GAC, GGC, CAC, AAC or AGC; R'_2 is AG; TTTG is present at +8 to +11; and R'_1 is G. An I-CreI meganuclease variant that cleaves this sequence could be produced according to the method of the invention and, thus, such a variant is within Precision's claim construction. Collectis's proposed claim construction, however, also includes I-CreI variants that cleave the following target sequence:



where each "N" can be any of the four possible nucleotides. The difference is claim scope should be apparent. Precision submits that nothing in the specification of the '372 Patent suggests such a broad construction of "modified specificity" and, therefore, Collectis's proposed construction should be rejected.

D. “A44/A68/A70 . . . T44/S68/K70” (Claims 5, 23, 41)

Claim Term	Collectis’s Proposed Construction	Precision’s Proposed Construction
“A44/A68/A70 . . . T44/S68/K70”	The nomenclature “X”44/“Y”68/“Z”70 means a variant monomer having amino acid residues, “X,” “Y” and “Z” at position 44, 68 and 70 with reference to the amino acid numbering of SwissProt accession number P05725 or pdb accession code 1g9y	The nomenclature “X”44/“Y”68/“Z”70 means a variant having amino acid residues “X,” “Y” and “Z” at positions corresponding, respectively, to positions 44, 68 and 70 of a wild-type monomer from I-CreI

1. Key Issues

Precision’s and Collectis’s proposed claim constructions are fundamentally very similar, but Collectis’s proposed construction (a) imports the word “monomer” into the construction without any basis, and (b) needlessly recites “positions . . . with reference to the amino acid numbering of SwissProt accession number P05725” rather than simply reciting “positions . . . of wild-type I-CreI.” The parties have agreed that the term “wild-type monomer of I-CreI” means “a monomer having the amino acid sequence of SwissProt accession number P05725 or pdb accession code 1g9y.” Therefore, Precision submits that this aspect of Collectis’s construction is unnecessarily complicated and would not aid the jury in interpreting the claims.

2. Collectis’s Construction Should Be Rejected

Because it needlessly incorporates the term “monomer” and is unnecessarily complicated, Collectis’s proposed claim construction should be rejected.

E. “single-chain chimeric meganuclease comprising [a] fusion of [two monomers]” (Claims 13-18, 31-36, 49-54)

Claim Term	Collectis’s Proposed Construction	Precision’s Proposed Construction
“single-chain chimeric meganuclease comprising [a]	a meganuclease in the form of a single protein comprising a first monomer fused to a second	a meganuclease in the form of a single polypeptide comprising a first monomer fused to a second monomer

fusion of [two monomers]”	monomer	
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Collectis’s and Precision’s proposed claim constructions differ by a single choice of words: “protein” or “polypeptide.” Although it is true that polypeptides are proteins and proteins are comprised of polypeptides, a protein can include one *or more* polypeptides (*i.e.*, multiple amino acid chains), whereas a polypeptide is a single amino acid chain and . A single-chain meganuclease is, by definition, a single polypeptide chain (single chain of amino acids). It is therefore more accurate and meaningful to describe a single-chain meganuclease as a single polypeptide rather than a single protein. (Seligman Decl., ¶¶ 63-64.) Because it describes a single-chain meganuclease as a single protein rather than a single polypeptide, Collectis’s proposed claim construction is unnecessarily imprecise and should be rejected.

F. “variant of the wild-type monomer from I-CreI” (Claims 9, 10, 13, 15, 25, 27, 28, 31, 33, 34, 43, 45, 46, 49, 51, 52)

Claim Term	Collectis’s Proposed Construction	Precision’s Proposed Construction
“variant of the wild-type monomer from I-CreI”	a mutant monomer of I-CreI, which when in dimeric form, retains the ability to cleave DNA	Indefinite under 35 U.S.C. § 112, ¶ 2

1. Key Issues

The claim terms “monomer according to claim 1” and “*variant* of the wild-type monomer from I-CreI” must have different meanings under the doctrine of claim differentiation because they are used as alternatives in claims 7, 25, 43, 13, 31, and 49.⁸ *Helmsderfer v. Bobrick Washroom Equipment, Inc.*, 527 F.3d 1379, 1382 (Fed. Cir. 2008) (“Our precedent instructs that different claim terms are presumed to have different meanings.”); *Bancorp Servs., L.L.C. v.*

⁸ Compare also claims 8 v. 10, claims 26 v. 28, claims 44 v. 46, claims 14 v. 16, claims 32 v. 34, and claims 50 v. 52.

Hartford Life Ins. Co., 359 F.3d 1367, 1373 (Fed. Cir. 2004) (“[T]he use of both terms in close proximity in the same claim gives rise to an inference that a different meaning should be assigned to each.”). The term “variant of the wild-type monomer from I-CreI,” however, is not defined anywhere in the specification or claims, nor does it have an accepted meaning in the art. (Seligman Decl., ¶¶ 65-67.) As such, a person of skill in the art would not be reasonably apprised of the scope of the invention. See *Talecris Biotherapeutics, Inc. v. Baxter Int’l, Inc.*, 510 F. Supp. 2d at 359 (quoting *Miles Labs., Inc. v. Shandon, Inc.*, 997 F.2d 870, 875 (Fed. Cir. 1993)). Therefore, Precision submits that the term is indefinite under 35 U.S.C. § 112, ¶ 2.

2. Collectis’s Construction Should Be Rejected

In addition to having no support in the specification or claims and no accepted meaning in the art, Collectis’s proposed construction does nothing to delineate the bounds of the claim term. Indeed, it is as vague and indefinite as the claim language itself and should be rejected.

G. “wild-type monomer from I-DmoI” (Claims 11, 12, 13, 17, 18, 29, 30, 31, 35, 36, 43, 47, 48, 49, 53, 54)

Claim Term	Collectis’s Proposed Construction	Precision’s Proposed Construction
“wild-type monomer from I-DmoI”	a naturally occurring amino acid sequence from I-DmoI that has the ability to cleave DNA when in dimeric form with a monomer of I-CreI	a meganuclease monomer having the amino acid sequence of PDB accession number 1b24

1. Key Issues

Although the parties have agreed upon a construction of the term “wild-type monomer from I-CreI” and Precision has proposed a construction of “wild-type monomer from I-DmoI” that is parallel, Collectis has proposed a construction of “wild-type monomer from I-DmoI” that includes an extraneous and logically indefensible limitation that it “has the ability to cleave DNA when in dimeric form with a monomer of I-CreI.”

2. Precision's Construction is Supported by the Accepted Meaning in the Art

There is no definition of the term "wild-type monomer from I-DmoI" in the specification of the '372 Patent, and no sequence is provided for the protein. However, there is a reference at col. 3, ll. 17-19 to two publications, Chevalier *et al.* (2002) and Epinat *et al.* (2003), which disclose hybrid meganucleases produced by fusing part of I-DmoI with part of I-CreI. Both of these papers cited to PDB accession number 1b24. Therefore, Precision's proposed construction, like the agreed upon construction for wild-type I-CreI, defines wild-type I-DmoI in terms of a database accession number known and accepted in the art. (Seligman Decl., ¶¶ 68-69.)

3. Collectis's Construction Should Be Rejected

Collectis's proposed construction should be rejected not only because it fails to properly define wild-type I-DmoI by reference to an accepted amino sequence for the protein, but because it incorporates an extraneous and logically indefensible limitation that it "has the ability to cleave DNA when in dimeric form with a monomer of I-CreI." First, there is no reason to reference I-CreI in a definition of I-DmoI: They are distinct proteins from different species and do not interact in nature. (Seligman Decl., ¶ 69.) More important, although I-CreI is a mono-LAGLIDADG meganuclease that forms homodimers in nature, wild-type I-DmoI is a di-LAGLIDADG meganuclease that does not form dimers in nature. (*Id.*) Thus, Collectis's suggestion that a monomer of I-DmoI can form a dimer with I-CreI is illogical. Accordingly, Collectis's proposed construction should be rejected.

H. "variant of the wild-type monomer from I-DmoI" (Claims 12, 13, 18, 30, 31, 36, 43, 48, 49, 54)

Claim Term	Collectis's Proposed Construction	Precision's Proposed Construction
"variant of the wild-type monomer from I-	a mutant monomer of I-DmoI that has the ability to cleave DNA when in dimeric form with a monomer of	Indefinite under 35 U.S.C. § 112, ¶ 2

DmoI”	I-CreI	
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1. Key Issues

Although the term “wild-type monomer from I-DmoI” has an accepted meaning in the art, the term “variant of the wild-type monomer from I-DmoI” does not, nor is it defined anywhere in the specification or claims. (Seligman Decl., ¶¶ 70-71.) A person of ordinary skill would not be able to determine from the intrinsic evidence what polypeptides would or would not qualify as “variants” of wild-type I-DmoI, nor is there an ordinary meaning upon which the skilled artisan could rely. *See Honeywell Int’l, Inc.*, 341 F.3d at 1338. Therefore, Precision submits that the term is indefinite under 35 U.S.C. § 112, ¶ 2.

2. Collectis’s Construction Should Be Rejected

Collectis’s proposed construction has no support in the intrinsic evidence and no accepted meaning in the art, nor does it apprise one of skill in the art of the scope of the claim term. Accordingly, Collectis’s proposed construction should be rejected.

V. CONCLUSION

For the foregoing reasons, Precision respectfully requests that the Court construe the disputed claims of the '372 Patent as proposed by Precision herein.

Respectfully submitted,

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CERTIFICATE OF SERVICE

I, David E. Moore, hereby certify that on August 15, 2012, true and correct copies of the within document were served on the following counsel of record at the addresses and in the manner indicated:

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